REMARKS

1. Formal Matters

1.1. Information Disclosure Statement

In the Oct. 11, 2007 office action, the Examiner stated that References BC and BD from the December 16, 2005 IDS were not considered because these references were "not translated".

We responded to this position in section 5.2 of the last amendment (March 11,2008). The new action does not respond to this, positively or negatively. We reiterate that the examiner's failure to consider these references was improper. For the convenience of the examiner, we quote the discussion from the prior amendment:

> Applicants are not required to provide an English translation unless a translation is already in their possession or control, or readily available to applicants. See 37 CFR 1.99(a)(3)(ii). No such translation is available, i.e., applicants would have to order and pay for such a translation. All that is otherwise required is a "concise explanation of the relevance" of the reference, see (3)(i). Reference BC includes an internal abstract which is deemed to satisfy the "concise explanation" requirement. As to reference BD, we enclose an abstract prepared by the applicants' European attorney.

If the examiner fails to consider references BC and BD in response to the present paper, then we will have to

take the issue up on petition.

1.2. Restriction/Election

We are in agreement with the examiner that the issue of whether the withdrawn claims should be rejoined turns on whether the prior art rejection is overcome. Naturally, we are of the view that the prior art rejection is not well taken, see section 2 below, and hence the withdrawn claims should be rejoined. We merely take this opportunity to remind the examiner that we are seeking rejoinder of those claims.

1.3. Overview of Claim Amendments

Claim 1, as examined, required that the composition comprise one or more purified flavonoids, purified menthol, and pharmaceutically acceptable excipients. Claim 1 has been amended to delete the superfluous reference to excipients (the claim being open in form), and to provide that the "purified menthol" is "in a state of purity such that the purified menthol has an antiviral effect on rhinovirus in WISH cells".

The present application reports applicant's discovery that menthol has an antiviral effect against rhinovirus (the common cold virus), it doesn't merely relieve symptoms such as congestion. See page 9, lines 6-7, 16-18; page 12, line 20 to page 13, line 19.

It appears that the antiviral effects of menthol are both indirect, that is, a potentiation of the antiviral activity of the interferon system as shown in Figs. 1A and 1B, see discussion at page 34, line 29 to page 35, line 20; and direct, see Figs. 2A and 2B, and discussion at page 35, line 27 to page 36, line 2. See also page 30,

lines 1-3 of Berg, WO 02/09699.

Thus, at page 36, lines 4-11, the specification declares:

> Conclusion of Figures 1A -2B: The above described experiments demonstrate that menthol has a direct effect on the growth of rhinoviruses, per se, and thus can be considered to exert antiviral activity in man infected with rhinoviruses or other related upper respiratory viruses known to induce the common cold syndromes.

See also Figures 1A-2B; page 7, lines 18-30.

A method of determining a direct antiviral effect (the MTS method) is first referred to at page 22, lines 5-12 and is further described at page 33, line 30 to page 34, line 13. The recitation of WISH cells is based on the above.

Claims 13 and 91 have been amended to correct a typographical error.

New claim 93 combines the limitations of claims 87 (menthol at least 90% pure) and 91 (absence of specified compounds found in peppermint oil).

New claims 94 (dependent on 1) and 95 (dependent on 87) require that the purified flavonoids themselves not have any direct antiviral activity in vitro. Basis is at page 17, lines 17-18; page 21, lines 24-33; page 22, line 24 to page 23, line 17.[1]

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[1] According to Berg, WO 02/09699, the flavonoids troxerutin and Veneruton do not have direct (page 29, lines 18-19) or indirect (IFN-system potentiation) antiviral activity (page 30, lines 9-14), whereas quercetin has a moderate direct antiviral activity (page

The importance of the IFN-system in the innate human response against viral infections is discussed at e.g. page 4, lines 4-13. We have previously alluded to data, new to this application, showing that purified menthol potentiates the IFN-mediated antiviral activity in vitro.

In Example 3, applicants report the new finding that peppermint oil depresses the IFN-system per se, see particularly page 37, line 24 to page 38, line 3. Use of purified menthol in place of peppermint oil thus avoids this depression, and indeed potentiates the IFN-system in vitro.

New claims 96 (dependent on 1) and 97 (dependent on 93) provide that "said composition does not increase the growth of rhinoviruses and/or does not down-regulate the protective action of the natural, human leukocyte interferon system." We have already alluded to the negative effect of peppermint oil on the IFN-system. Applicants have also shown that peppermint oil potentiates the production of rhinovirus, ee page 37, lines 4-22.

New claim 98 requires that the menthol be 98% pure, with basis at page 10, lines 8-27.

New claim 99 requires that the composition have a greater antiviral activity than an otherwise identical composition comprising peppermint oil instead of purified menthol. This is based on the clear teaching that purified menthol provides an antiviral effect whereas peppermint oil has a negative effect as explained above.

New claim 100 requires that the composition has less cytotoxicity than an otherwise identical composition

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29, lines 19-20). Other antiviral flavonoids are known, see WO 01/03681, cited at page 6, lines 11-12 here, and discussed also by Berg, WO 02/09699.

comprising peppermint oil instead of purified menthol. It is shown at page 36, lines 16-22 that peppermint oil is "rather toxic to WISH cells".

New claim 101 combines the limitations of claims 99 and 100.

New claim 102 requires that the composition **has greater antiviral activity than do the purified flavonoids alone.** If the flavonoid is one which does not itself have an antiviral effect, then the antiviral activity is necessarily attributable to the purified menthol. If any of the flavonoids in the composition are antiviral flavonoids, then -- in view of applicant's discovery of the antiviral activity of menthol -- the skilled worker, reading the specification, would expect there to be an additive effect from the combination and thus that the combination has a greater antiviral activity than does the purified flavonoid alone. However, knowing only of the prior art, which did not attribute any antiviral activity to menthol, the person of ordinary skill in the art would not have expected the composition to have greater antiviral activity than does the purified flavonoid alone.

New claims 103 and 104 are similar, except that they compare the claimed composition to an otherwise identical one in which the purified menthol is replaced with peppermint oil (103), or in which the purified menthol is simply omitted (104).

New claim 105 requires that the purified menthol is capable of at least about 50% reduction in rhinovirus in WISH cells, measured as a reduction in cytopathic effect. For basis, see page 13, lines 15-19, and page 35, line 30 to page 36, line 2.

New claim 106 requires that, after 48 hours, the

composition achieves on average at least a 75% decrease in symptom score. For basis, see page 32, line 35 to page 33, line 1. Note that the average reduction achieved with "menthol" lozenges was 77% (page 41, line 11) and that achieved with peppermint oil lozenges was only 71% (page 42, line 2).[2]

New claim 107 requires that, after 72 hours, the composition achieves on average at least a 85% decrease in symptom score. For basis, see page 33, lines 5-6. Note that the average reduction achieved with "menthol" lozenges was 90% (page 41, line 12) and that achieved with peppermint oil lozenges was only 80% (page 42, line 3).

New claim 108 requires that, after 48 hours, the composition achieves a greater average decrease in symptom scores than that achieved with an otherwise identical composition which comprises peppermint oil, rather than purified menthol. The basis is the same as for claim 106, and in addition, please note the teaching at page 6, lines 26-28 that "pharmaceutical compositions comprising flavonoid and purified menthol are more efficient than similar compositions comprising other flagrances in the treatment of common cold and related conditions." The "other flagrances" quite clearly include peppermint oil,

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[2] For the compositions of the two lozenges, see page 20, lines 20-31. The menthol lozenges contained 4-5mg (-) menthol and 50 mg troxerutin, whereas the peppermint oil lozenges contained 50 mg Veneruton and 8 mg peppermint oil. (The PCT application as filed said 4-5 mg of menthol, but a request for correction was filed during the international phase. Counsel needs to investigate whether this request was granted and, if not, file a supplemental amendment to correct the specification here.) WO 02/09699 states at page 8, lines 11-12 that Veneruton is a mixture of hydroxyethylrutosides of which about 50% is troxerutin.

see page 5, line 33.

In like manner, new claim 109 addresses the comparative symptomatic relief after 72 hours, with the same basis as for claim 107.

2. Prior Art Issues

Claims 1, 3, 5-27 and 84-92 stand rejected as obvious over Berg, WO 02/09699. This rejection is respectfully traversed.

2.1. There is a procedural problem with the rejection. While the only reference formally relied on is Berg, on page 4, in the response to arguments, the examiner is clearly relying on WO 01/03681 and Eccles (1994). If the examiner is going to continue to argue that those references support a finding of obviousness, then they should formally be relied upon as part of the statement of the rejection.

2.2. Claim 1, as examined, was directed to "A pharmaceutical composition comprising one or more purified flavonoids; and **purified menthol**; and pharmaceutically acceptable excipients." It is now amended to add a functional limitation to the purified menthol, i.e., that it be in a state of purity "such that the purified menthol has an antiviral effect on rhinovirus in WISH cells".

Claim 87 requires that the purified menthol be at least 90% pure, and this limitation is of course incorporated into any claim dependent claims thereof. New claim 98 requires that the purified menthol be at least 98% pure.

Other claims contain compound-specific purity limitations: "essentially free of components of peppermint oil other than menthol" (claim 86) or "essentially free of

one or more selected from the group consisting of menthone, menthyl acetate, limonene and neomenthol" (claim 13) or "essentially free of other terpenes than menthol" (claim 12), or the further compositions of claims 90-92. Claim 93 combines limitations of 87 and 90, and several new claims are dependent on 93.

Other new claims recite further functional limitations, either absolute or by way of comparison with a comparable composition omitting the purified menthol or containing peppermint oil in place of the purified menthol.

2.3. We begin by reviewing the prior interchange between us and the examiner. In the Oct. 11, 2007 rejection, Berg was said to teach compositions comprising purified flavonoids and zinc metal complexes/salts, and optionally peppermint oil. The Examiner asserted that the "major constituent" of peppermint oil is menthol and held that it would have been prima facie obvious to modify Berg's composition by replacing the peppermint oil with purified menthol.

In our March 11, 2008 amendment, we argued that peppermint oil, rather than consisting mainly of menthol, comprises a number of different components, and thus "purified menthol" may have different biological properties than peppermint oil.

We are not aware of any authority which asserts that peppermint oil contains 90% or more menthol as required by claim 87, and exhibits 1 and 2, attached to the last amendment, suggest that the menthol content is quite a bit lower than 90%.

The Examiner argued, in support of the finding of

prima facie obviousness, that changing the level of purity of the menthol is an obvious modification, and the mere optimization of a variable, and that the motivation would be to obtain a purer composition.

The instant claims, of course, are not to a purified menthol composition, but rather to the combination of the purified menthol with a purified flavonoid. It is therefore necessary to inquire into why Berg adds peppermint oil to his composition, and whether, in the context of the disclosed purpose of the peppermint oil, whether the art would have found it obvious to replace the peppermint oil with a purified menthol.

In Berg et al., peppermint oil is added to the pharmaceutical compositions merely for flavoring purposes (see p. 24, l. 1-6). Berg et al does not suggest that peppermint oil has any <u>therapeutic value</u> in relation to treatment of common cold. Consequently, Berg et al nowhere teaches that any components of peppermint oil, such as menthol, would have therapeutic value in treatment of common cold.

Nor does Berg suggest that the flavor of the composition would be improved if peppermint oil were replaced with purified menthol. Replacing peppermint oil with purified menthol would result in the loss of all of the lesser components which contribute to the overall taste of peppermint oil, see prior Exhibit 5.

If the person of ordinary skill in the art was indeed trying to improve the flavor of the composition by replacing the peppermint oil with one of its purified constituents, it does not necessarily follow that the desired constituent would be the menthol. It could, instead, be the menthone, or even a more minor constituent

of peppermint oil. Nowhere does Berg state that he is adding peppermint oil for the sake of its menthol content.

Nor would the person of ordinary skill in the art necessarily believe that it was necessary or desirable to go to the expense of purifying the menthol to the point recited in the cited claims.

In addition, replacing peppermint oil with purified menthol could have been thought undesirable in other ways. For example, Sturtz, Plant Patent 08645, LOW MENTHOL MINT PLANT MENTHA SPICATA L. `EROSPICATA` teaches that a peppermint-tasting essential oil with a low menthol content is desirable "because menthol is an alcohol that irritates nasal, oral and gastrointestinal epithelium." Sturtz offers, in its place, an oil high in menthone.

2.4. In the "response to arguments", the Examiner in fact fails to address several of the arguments recapitulated above. In particular, while the examine acknowledges that Berg teaches use of "menthol" (sic, should be "peppermint oil", which inherently contains menthol) for flavoring, the examiner fails to consider whether the art would have considered that the replacement of peppermint oil with menthol would have been discouraged because it would have been expected to impair the flavor of the composition (by loss of the other peppermint oil components) or to result in nasal, oral or gastronintestinal irritation.

2.5. Instead, the examiner argues that both flavonoids and menthol are widely used in cold remedies for the purpose of treating common cold. It is not

entirely clear from the examiner's analysis whether he is asserting that they are used in combination in this way, or individually.

It is important to distinguish between mere use of menthol in a cold remedy and use with the expectation that it will have a therapeutic effect.

In support of the assertion, the examiner points to WO01/03681 and Eccles' review article. While WO 01/03681 certainly teaches use of flavonoids to treat viral infections, searching the description and claims electronically did not reveal any reference to "menthol" or "peppermint" per se. Hence, at first blush, WO01/03681 doesn't appear to show use of menthol in cold remedies, even as a flavoring agent let alone as an antiviral agent.

Eccles' review article discusses the nasal decongestant and antitussive activities of menthol. These are pharmaceutical activities, but it is important to note that they aren't antiviral activities.

Claim 1, as amended, requires that the menthol be purified to a state of purity such that the menthol has a direct antiviral activity. We know from applicants' experiments that while this is true of purified menthol, it is not true of peppermint oil which indeed actually promotes rhinovirus growth (if administered under conditions in which it isn't toxic to the cells).

2.6. We note that while the examiner made a holding of prima facie obviousness, the examiner failed to consider whether the unexpectedly superior results shown by applicant's experiments (discussed on pp. 23-26 of the last amendment) would rebut that holding.

In those experiments, fundamental differences between pure menthol and peppermint oil are disclosed, especially

regarding biological properties in respect of virus replication and the HuIFN-alpha system:

1. Menthol has a direct antiviral activity vs. rhinovirus in cell culture experiments. As demonstrated in Figures 2A and 2B cells treated with menthol (0.04%) were protected significantly to a higher degree (approx. 25%) compared to untreated cells (statistically significant) - cf. this patent appl., Example 2, p.34, l.25 - p.36, l.11.

2. Menthol is able to potentiate the human interferon-alpha system (interferon is produced by the host during the rhinovirus infection). This is demonstrated in Figures 1A and 1B, wherein an increased cell viability is observed for cells treated with menthol+interferon rather than just interferon - cf. Example 2, p.34,l.25 - p.36,l.11.

3. Peppermint oil was shown to be rather toxic to the cells. Similar experiments as described above under point 2. were undertaken using peppermint oil. However, the peppermint oil appears to be toxic for cells (see example 3).

4. Peppermint oil increases the production of rhinovirus in cell culture experiments. The results in Figure 3A demonstrate that the presence of the volatile part of Peppermint oil (PPO) increases the amount of virus produced. In contrast to the virus control dose-response curve (HRV control), the virus dose-response curve with PPO is independent of the virus.

5. Peppermint oil depresses the human-alpha interferon system in cell culture experiments cf. the description in the Appl. p.37,.24-p.38,l.3.

Accordingly, in contrast to peppermint oil, purified menthol has direct antiviral activity in vitro and is capable of potentiating the interferon alpha system. Thus use of purified menthol cannot be considered equivalent to use of peppermint oil, despite the fact that peppermint oil comprises menthol. The present application is the first showing that purified menthol has a specific antiviral activity.

In addition to the above-mentioned differences in biological activity in in vitro studies between menthol and peppermint oil, pharmaceutical compositions comprising purified menthol and flavonoid are significantly more efficient for treatment of common cold, than the pharmaceutical compositions described in the Berg reference.

As is apparent from Table 1, the over-all reduction in symptom score (SS) at day 3 corresponds to 90% reduction after treatment with Menthol+flavonoid. In contrast, the over-all reduction in symptom score after treatment with peppermint oil+flavonoid was merely 80% (see table 2).

In Berg, peppermint oil is added to the pharmaceutical compositions merely for flavoring purposes (see p. 24, l. 1-6). Berg nowhere discusses any advantageous effects obtained by addition of peppermint oil in relation to treatment of common cold. In particular, Berg nowhere describes what components of peppermint oil, if any, could be advantageous in treatment

of common cold.

A person skilled in the art seeking to provide improved pharmaceutical compositions for treatment of common cold would therefore based on Berg not have known or been led to believe that peppermint oil or any components thereof provides any advantageous effect. In particular, said skilled person could based on Berg not have reached the conclusion that pharmaceutical compositions comprising purified menthol in combination with flavonoids are superior over similar compositions comprising peppermint oil.

2.7. In the "response to arguments," the examiner also asserts that the applicant is trying to rigidly apply TSM, which is contrary to KSR, and under KSR, if the prior art fails to set forth TSM, other factors can be considered (and used against applicant).

The examiner is trying to knock down a straw man here. In KSR, the Supreme Court criticized certain per se TSM rules developed by certain panels of the Federal Circuit. It made it clear that there was still a place for TSM in obviousness analysis if TSM were flexibly applied. Flexible application means that the failure to find TSM doesn't automatically result in a finding of non-obviousness.

We respectfully urge that *KSR* did not overrule the Federal Circuit's "teaching-suggestion-motivation" test; it merely suggested that the particular Federal Circuit panel had, in that case, applied the TSM test in an overly rigid way. The Supreme Court conceded that "there is no necessary inconsistency between the idea underlying the TSM test and the Graham analysis". It said that the TSM

test may provide "helpful insights", as long as it is not converted it into a "rigid and mandatory formula"[3]. It noted (see e.g. 82 USQP2d at 1397) that it hadn't reviewed the TSM standard as more flexibly applied by the Federal Circuit in Dystar Textilfabriken GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1367, 80 USPQ2d 1641 (Fed. Cir. 2006) and Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1291, 80 USPQ2d 1001 (Fed. Cir. 2006).

Consequently, TSM can and should be applied here, provided that we avoid the errors noted by the Supreme Court: (1) not limiting the search for motivation to the problem which the patentee (applicant) was seeking to solve, (2) not limiting the search for combinable elements to those designed to solve the same problem, and (3) denigrating as "obvious to try" a search for a solution from among a small number of alternatives.

The Supreme Court acknowledged that a combination of known elements is not necessarily obvious, citing United States v. Adams, 383 U.S. 39, 148 U.S.P.Q. 479 (1966) and hence inquiry was necessary into whether there was "an apparent reason to combine the known elements in the fashion claimed by the patent in issue." Thus, under KSR there must still be a "reason to combine" the references, and the courts must also examine the result of the combination to see whether it exceeded expectations (i.e., yield more than just the "predictable results").

In a post-KSR decision, Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.,[4] the Federal Circuit

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[3] 550 U.S. ___, 127 S. Ct. 1727, 82 USPQ2d 1385, 1396 (2007).

[4] 492 F.3d 1350; 2007 U.S. App. LEXIS 15349; 83 U.S.P.Q.2D (BNA) 1169 (Fed. Cir. 2007).

reconciled KSR with the TSM test by flexibly applying TSM. The result was that it affirmed a district court holding that a patent claim was nonobvious. There is a class of drugs, thiazolidinediones (TZDs), which reduce insulin resistance. One such TZD is pioglitazone, the active ingredient in Takeda's ACTOS® drug, and the subject of the challenged claim.

Alphapharm asserted that the claimed pioglitazone was structurally obvious over a known TZD. The argument required that the person of ordinary skill in the art first select that known TZD (called "compound b" in the opinion) as the lead compound, and then make two chemical changes: 1) "homologation," replacement of the methyl group with an ethyl group, and 2) "ring-walking," movement of that ethyl group from the 6-position to the 5-position on the ring.

The district court had found that the skilled worker would not have selected "compound b" as a lead compound for further development. Not only were there prior art patents with claims for TZDs which covered hundreds of millions of compounds, there was a nonpatent reference in which compound b was compared with several other TZDs and was not one of the three TZDs which that reference identified as being the "most favorable." The Federal Circuit agreed with this analysis.

The district court also was not persuaded that even if "compound b" were to be considered a "lead compound," that the skilled worker would have been motivated to make the two required chemical changes because there would not have been a reasonable expectation that either change would have reduced the toxicity or increased the efficacy of compound b.

The district court also considered the low toxicity of pioglitazone to be an unexpected result, given the significant side effects induced by "compound b."

How did the Federal Circuit reconcile its decision with the analytical framework established by KSR? First, under KSR, there must still be a reason to combine the elements; in the case of a new chemical compound, a reason to modify a known compound so as to arrive at the claimed one. In seeking to determine whether there was such a reason, it could apply its traditional TSM test provided it did so in a "flexible" manner.

Here the allegedly obvious combination of elements is a combination of compounds, rather than a combination of chemical moieties within a single compound, but a flexible TSR analysis is still proper.

Secondly, in Takeda there weren't merely a "finite" [sic, "small"] number of "identified, predictable solutions," such that the routineer would be motivated to pursue all the "known options within his or her technical grasp." It was thus not an acceptable obvious-to-try case.

The situation here is analogous. While peppermint oil was used in the composition page 26 of the reference, page 24, line 6 implies that sorbitol could be used in place of peppermint oil, and page 23, line 27 makes generic reference to "flavors". There are a large number of flavoring alternatives to peppermint oil, and for that matter a large number of compounds with decongestive activity as well or better established than that of menthol. In searching for an improvement over the disclosed flavonoid-peppermint oil combination, one wouldn't be forced, through exhaustion of a small number of options, to pick flavonoild-menthol.

Thirdly, in Takeda there were "negative properties" attributable to what was presumably the closest prior art compound. Surprisingly, the appellate court didn't point out the importance of such "negative properties" in Adams. Here, applicants have identified negative properties associated with the peppermint oil component of the Berg reference composition.

2.8. *Secondary Considerations*. Moreover, in KSR, the Supreme Court did not repudiate the well-established use, in Graham type obviousness analysis, of the so-called "secondary considerations."

In *Graham v. John Deere & Co. Of Kansas City*, 383 US 1, 17-18, 148 USPQ 459 (1966), the Supreme Court said that "such secondary considerations as commercial success, **long felt but unsolved needs**, faiure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter of the invention. As indicia of obviousness or nonobviousness, these inquiries may have relevancy." MPEP 2141(I) lists "evaluating evidence of secondary considerations" as a required factual inquiry.

Thus, the courts have recognized that a long-felt but unsatisfied need, which was at last satisfied by the claimed invention, is an indication of non-obviousness.

KSR accepted the relevance of secondary factors. However, on the facts presented to it, the KSR court agreed with the district court that "secondary factors" did not help the patentee.

In Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc., 81 USPQ2d 1324 (Fed. Cir. 2006), olanzapine was held to have satisfied a long-felt but

unsolved need (felt from 1975 to 1990) for a safe atypical antipsychotic.

That there is a long-felt but not fully satisfied need for agents which, rather than alleviate symptoms, attack the rhinoviral cause of the common cold, can hardly be doubted. See discussion in Berg, pages 1-6.

Eccles (Ref. AZ) teaches that menthol was already used, by 1890, in the treatment of "diseases of the upper air passages", and that it has been widely used "for the relief of common cold symptoms such as nasal congestion and cough." Despite this long usage, it does not appear that it was ever suggested that menthol might have an actual antiviral effect, and indeed Eccles notes that "there is little hard scientific evidence to support any nasal decongestant or antitussive activity."

Fisitin and flavone are examples of flavonoids. According to the Merck Index, the earliest references for the flavonoid fisetin are Chevreul, Lecons chim appl a la teint (1833) and J SChmid, Ber. 19, 1734 (1886), and the earliest references for the flavonoid flavone are Feuerstein, Kostanecki, Ber. 31, 1757(1898) and Kostanecki, Tambor, Ber. 33, 330 (1900). Thus, flavonoids have been known since at least 1833!

Nonetheless, as of applicants' Danish priority date (2002), there still had not been any teaching in the art that the combination of a purified menthol and a purified flavonoid would be useful in the treatment of the common cold.

2.9. *Unexpected Results.* Nor did KSR hold that the presence of synergism, or other forms of unexpectedly superior result, could no longer rebut a finding of prima

facie obviousness.

In A&P Tea, cited by the Examiner in the previous Office Action, the Supreme Court remarked, "Elements may, of course, especially in chemistry or electronics, take on some new quality or function from being brought into concert, but this is not a usual result of uniting elements old in mechanics."

The present invention is drawn to a chemical composition and the menthol element has indeed taken on a new quality or function, displaying, in its combination with the flavonoid, an antiviral effect. In contrast, its known function in the cited prior art had been merely to enhance the flavor of an ingested composition.

Indeed, it is fair to characterize the result of the combination of purified menthol with purified flavonoid as being synergistic; no "synergistic result" was argued in the Anderson's Black Rock case which the examiner continues (OA page 3, third to last line) to mis-cite as In re Anderson, see 163 USPQ at 674. In Sakraida, a "synergistic result" was suggested, but the Supreme Court decided that this was a mis-characterization, as each of the elements was "performing the same function it had been known to perform." Purified menthol has not previously been known to have an antiviral effect, whether alone or in combination with a purified flavonoid.

The antiviral effect contributed by the menthol was an unexpected and unpredictable one which supports a conclusion of non-obviousness (see above where the differences between menthol and peppermint oil is discussed).

Since the menthol of peppermint oil was not known to

have any antiviral effect, the peppermint oil would not have been expected to enhance the antiviral activity of the flavonoid or flavonoid-zinc composition, merely to improve its flavor.

Hence, the art would not have expected the applicants' purified menthol-flavonoid (with or without zinc) composition to be superior in antiviral activity to the comparable peppermint oil composition. The experimental results delineated in the specification shows that it is indeed superior, and we have already explained why that superiority would have been considered unexpected.

Anderson's Black Rock and Sakraida, on which the examiner continues to rely, stated that if a combination is synergistic, that is, the effect of the combination is greater than the predictable additive effect of its components, the combination is patentable. Since the menthol in the prior art composition was not known to have any antiviral effect, the predictable additive effect of the claimed composition would have been equal to the effect of the flavonoid/zinc combination alone. The increased effect observed by applicants is therefore an example of patentable synergy.

The Federal Circuit has repeatedly held that a case of prima facie obviousness can be rebutted by a showing of unexpectedly superior results. See, e.g., In re Sernaker, 217 USPQ 1, 5 (Fed. Cir. 1983); In re Chupp, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987); Kao Corp. v. Unilever US, Inc., 78 USPQ2d 1257 (Fed. Cir. 2006). Such results have been disclosed in the specification.

The unexpected superiority of (+)-citalopram over (-)-citalopram as a serotonin uptake inhibitor contributed

to the holding that a claim to substantially pure (+)-citalopram was non-obvious. Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc., 84 USPQ2d 1099 (Fed. Cir. 2007).

In conclusion, a person skilled in the art seeking to provide improved pharmaceutical compositions for treatment of common cold would therefore not have been led to believe by Berg et al. that peppermint oil, or any components thereof, provide any advantageous effect other than improved flavor. In particular, said skilled person could not, based on Berg et al, have reached the conclusion that pharmaceutical compositions comprising purified menthol in combination with flavonoids are superior in antiviral activity over similar compositions comprising peppermint oil in combination with flavonoids. The superiority which they in fact manifested was thus unexpected and deserving of patent protection.

Respectfully submitted,

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